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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/554,921	10/31/2005	Hiroshi Miura	280271US0X PCT	2311

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EXAMINER	
PALENIK, JEFFREY T	
ART UNIT	**PAPER NUMBER**
1615	

NOTIFICATION DATE	DELIVERY MODE
12/02/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/554,921	MIURA ET AL.	
	Examiner	Art Unit	
	Jeffrey T. Palenik	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-35* is/are pending in the application.

4a) Of the above claim(s) *25-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of Applicants' Amendments and Remarks filed 24 July 2008. The Examiner acknowledges the following:

Claim 21 has been amended. Where support for the amendments was not expressly provided, it was found either within Applicants' disclosure and/or originally filed claims. The Examiner acknowledges that no new matter has been added to the claims.

Claims 25-35 which were previously only withdrawn from consideration currently remain so.

No claims have been cancelled and no further claims have been added.

Thus, claims 21-24 still represent all claims currently under consideration.

INFORMATION DISCLOSURE STATEMENT

No new Information Disclosure Statement (IDS) have been submitted for consideration.

WITHDRAWN OBJECTIONS/REJECTIONS

Rejection under Nonstatutory Obviousness-Type Double-Patenting

Applicants' amendments to both the instant claim 21 and copending claim 1 of Application number 10/551,901 differentiate the instantly claimed porous materials used in the respective applications. The instant claim 21 has been amended such that it recites using porous silica material having specific properties (i.e. pore diameter) which match those of the porous silica material expressly excluded from claim 1 of the copending '901 application. Thus, said rejection has been **withdrawn**.

Rejection under 35 USC 112

Applicants' amendment to further define the phrase, "extremely poorly water-soluble drug" within claim 21 renders moot the rejection to claims 21-24, under 35 USC 112, second paragraph. Thus, said rejections have been **withdrawn**.

Rejection under 35 USC 102(b)

Applicants' amendments to the instant claims, namely claim 21, renders moot the rejection to claims 21-24 under 35 USC 102(b) as being anticipated by Ohkuchi et al. (USPN 6,348,468). Thus, said rejection has been **withdrawn**.

Rejection under 35 USC 103(a)

Applicants' amendment to the instant claims, namely claim 21, render moot the rejection to claims 21-24 under 35 USC 103(a) as being unpatentable over Mandel et al. (WO 02/20624) in view of Tsutomu et al. JP-2002-345940 (machine translation), Ohkuchi et al. (U.S. Patent 6,348,468) and in further view of defined products available from Sigma-Aldrich. Thus, said rejection has been **withdrawn**.

NEW REJECTIONS

In light of Applicants' amendments, most notably to claim 21, the following rejections have been newly added:

CLAIM REJECTIONS - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 21 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Verhoff et al. (US Pre-Grant Publication N° 2002/0047058).

The instantly amended claims are now directed to a composition comprising a very low water-soluble drug and a porous silica material, wherein said drug has a solubility of less than 10 μg/mL at 25°C prior to treatment and said porous material has the recited properties (claims 21 and 22). The limitation whereby said composition is "produced by treating a mixture … with a supercritical or subcritical carbon dioxide fluid" is still interpreted by the Examiner as a product-by-process limitation which holds no patentable weight (MPEP §2113), particularly in absence of evidence to the criticality of the limitation. With regard to the limitations recited in claim 21, which states that said drug "has a solubility of less than 10 μg/mL at 25°C prior to treatment"; until some material difference in the properties of the composition are demonstrated, said limitation is considered by the Examiner to be directed toward "an extremely poorly water-soluble drug" (i.e. a water-insoluble or poorly-soluble drug), which is instantly claimed. With regard to the limitations recited in claim 2, which stating that "the porous silica material has a specific surface area of 100 to 2,000 m^2/g"; until some material difference in the properties of the porous material of the composition or in the composition itself are demonstrated, said limitation

is considered by the Examiner to be directed towards the silica material of the instantly claimed composition.

Verhoff et al. teach the preparation of a drug product (e.g. composition) comprising a commixture of small particles of a solid substrate and small particles of a first material, the combination of which is treated (e.g. milled) in the presence of a fluid carrier (claim 1). Said solid substrate is further taught as either a poorly water-soluble or water-insoluble pharmaceutical agent (claims 5 and 6). The small particles of first material are further taught as consisting of silica or colloidal silica (claim 17). Verhoff expressly teaches using drugs which are insoluble in water. The term "insoluble" is interpreted by the Examiner as teaching zero solubility in water, which is less than the recited property limitation of the instantly claimed drug. Furthermore, the "fluid carrier" of claim 1, is further taught in ¶[0149] as comprising a single component or mixture or solution of one or more subcritical or supercritical fluids such as supercritical carbon dioxide.

CLAIM REJECTIONS - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 21-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Verhoff et al. (US Pre-Grant Publication N° 2002/0047058) in view of Takano et al. (USPN 6,753,330).

The instantly amended claims are directed to a composition comprising a extremely poorly water-soluble drug and a porous silica material, as discussed above. Claim 23 further limits the composition by reciting a weight ratio of the drug to the porous material ranging from 0.1:1 to 1:1,000. Claim 12 recites that the drug is the anti-rheumatic composition: 2-benzyl-5-(4-chlorophenyl)-6-[4-(methylthio)phenyl]-2H-pyradazin-3-one.

The teachings of Verhoff et al. are discussed above. Verhoff further teaches that the poorly-soluble/water-insoluble active agent may comprise drug classes such as anti-rheumatic agents ¶[0256] and claim 5. Preferred milling media compositions are taught as comprising adjustable concentrations of the solid substrate, fluid carrier and milling media bodies of a first

material depending upon the application ¶[0247]. For example, the ratio of the first material (e.g. silica or colloidal silica) to a second material is taught as ranging as broadly from 1:1000 to 1000:1.

Verhoff fails to expressly teach Applicants' claimed ratio range of drug to porous silica material, recited in claim 23, as well as either of Applicants' claimed drug species, recited in claim 24.

Takano et al. teach pharmaceutical solid dispersions comprising the compound: 2-benzyl-5-(4-chlorophenyl)-6-[4-(methylthio)phenyl]-2H-pyradazin-3-one (Abstract). Said compound is further taught not only as having a generally poor dissolvability in water but also as being of particular use as therapeutic agent for articular rheumatism (col. 1, lines 8-30).

Similar to Verhoff, Takano fails to expressly teach Applicants' claimed drug/porous silica material ratio ranging as instantly claimed.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare a composition comprising the combination of an extremely poorly water-soluble drug and a porous silica material as taught by Verhoff and as suggested by the combination of Verhoff and Takano, modify the ratio of drug to porous silica material, and produce the instantly claimed composition.

One of ordinary skill in the art would have been motivated to do this because Verhoff expressly teaches the instantly claimed silica/drug composition, including preparing said composition by milling in the presence of a fluid carrier such as supercritical carbon dioxide.

Though Verhoff does not expressly teach incorporating 2-benzyl-5-(4-chlorophenyl)-6-[4-(methylthio)phenyl]-2H-pyradazin-3-one as the poorly water-soluble active ingredient complexed in the preparation, the motivation to do so is provided by the fact that Verhoff does teach using active compounds such anti-rheumatic agents as the insoluble solid substrate (see ¶[0256] and claim 5). Coupled with the guidance of the invention to Ohkuchi, the skilled artisan would be well motivated to use the poorly water-soluble species of 2-benzyl-5-(4-chlorophenyl)-6-[4-(methylthio)phenyl]-2H-pyradazin-3-one in the invention to Verhoff and produce the instant invention.

The combined references do not expressly teach the ratio limitations of poorly-soluble drug to porous material, as instantly claimed by Applicants. Since the values of each parameter with respect to the claimed composition are adjustable, it follows that each is a result-effective parameter that a person having ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. In the instant case, the skilled artisan, would be highly motivated to adjust the aforementioned ratio in view of the teachings presented by Verhoff where it is discussed that the concentrations of the components in the preparation (i.e. the first material, the solid substrate and the milling media) can be optimized based on such requirements as milling performance and flow characteristics of the substrate to be milled ¶[0247]. Thus, absent some demonstration of unexpected results from the claimed parameters, optimization of any of these parameters would have been obvious at the time of Applicants' invention.

From the teachings of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the reference, especially in the absence of evidence to the contrary.

All claims have been rejected; no claims are allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey T. Palenik whose telephone number is (571) 270-1966.

The examiner can normally be reached on 7:30 am - 5:00 pm; M-F (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jeffrey T. Palenik/
Examiner, Art Unit 1615

/MP WOODWARD/
Supervisory Patent Examiner, Art Unit 1615